# Fish Oil Supplementation and Urinary Oxalate Excretion in Normal Subjects on a Low-oxalate Diet

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**OBJECTIVE** To determine if fish oil supplementation reduces endogenous oxalate synthesis in healthy subjects.

**MATERIALS AND METHODS** Fifteen healthy non–stone-forming adults participated in this study. Subjects first abstained from using vitamins, medications, or foods enriched in omega-3 fatty acids for 30 days. Next, they collected two 24-hour urine specimens while consuming a self-selected diet. Subjects consumed an extremely low-oxalate and normal-calcium diet for 5 days and collected 24-hour urine specimens on the last 3 days of this diet. Next, the subjects took 2 fish oil capsules containing 650-mg eicosapentaenoic acid and 450-mg docosahexaenoic acid twice daily for 30 days. They consumed a self-selected diet on days 1-25 and the controlled diet on days 26-30. Twenty-four-hour urine samples were collected on days 28-30. Excretion levels of urinary analytes including oxalate and glycolate were analyzed.

**RESULTS** Although there was a significant reduction in urinary oxalate, magnesium, and potassium excretions and an increase in uric acid excretion during the controlled dietary phases compared with the self-selected diet, there were no significant differences in their excretion during controlled diet phases with and without fish oil supplementation.

**CONCLUSION** These results suggest that fish oil supplementation does not reduce endogenous oxalate synthesis or urinary oxalate excretion in normal adults during periods of extremely low oxalate intake. However, these results do not challenge the previously described reduction in urinary oxalate excretion demonstrated in normal subjects consuming a moderate amount of oxalate in conjunction with fish oil. UROLOGY 84: 779–782, 2014. © 2014 Elsevier Inc.

Calcium oxalate is the most common type of kidney stones.[1] Increased urinary oxalate excretion is a risk factor for calcium oxalate kidney stone formation,[2-4] and small increases in urinary oxalate excretion are associated with significant increases in stone risk.[5] Urinary oxalate is derived from both dietary sources and endogenous synthesis.[6] It has been demonstrated that the administration of fish oil, a rich source of omega-3 fatty acids, reduces urinary oxalate excretion.[7-9] Siener et al[9] attribute this to an altered fatty acid pattern of membrane phospholipids and changes in oxalate transporter activity. This can result in altered gastrointestinal and/or renal oxalate handling and promote reduced urinary oxalate excretion. Another possibility is that fish oil supplementation promotes a reduction in endogenous oxalate synthesis. Fish oil has known anti-inflammatory properties, and the latter may be associated with a reduction in oxidative stress. Oxidative stress has been proposed to increase endogenous oxalate synthesis because of the conversion of the reactive dialdehyde, glyoxal, to glyoxylate, the immediate precursor of oxalate.[10] Herein, we report a study to assess whether fish oil supplementation reduces endogenous oxalate synthesis.

## MATERIALS AND METHODS

After study approval by the Wake Forest School of Medicine Institutional Review Board, 15 healthy non–stone-forming adults (average age, 25.3 ± 2.7 years; body mass index <30 kg/m$^2$; 8 men; and 7 women) were recruited to participate in this study. Potential subjects abstained from utilization of any supplements including vitamins, medications, or foods

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**Table 1.** Components of controlled diet

| Nutrient | Daily Content |
|---|---|
| Oxalate | 50 mg |
| Calcium | 1000 mg |
| Sodium | 3500 mg |
| Magnesium | 300 mg |
| Phosphorus | 1500 mg |
| Potassium | 3000 mg |
| Vitamin C | 125 mg |
| Fluids | 2.5 L |

enriched in omega-3 fatty acids and consumed a self-selected diet for 30 days and then collected two 24-hour urine specimens. These were analyzed for volume, creatinine, sodium, potassium, magnesium, calcium, oxalate, uric acid, phosphate, citrate, urea nitrogen, and Tiselius index for calcium oxalate. Urinary analytes other than oxalate were measured on a Beckman C5E analyzer (Beckman Coulter, Inc, Brea, CA). Oxalate was measured using a kit provided by Trinity Biotech (St. Louis, MO). The subjects then consumed a controlled low-oxalate normal-calcium diet for 5 days. Dietary components are listed in Table 1. This diet was intended to dramatically limit the contribution of dietary oxalate to the urinary oxalate pool. The meals were prepared in the metabolic kitchen of the Wake Forest Clinical Research Unit and were tailored to each subject's daily caloric needs. The participants collected 24-hour urine specimens on days 3-5 of the initial controlled diet phase. Next, the subjects began taking 2 fish oil supplement capsules containing 650-mg eicosapentaenoic acid (EPA) and 450-mg docosahexaenoic acid (DHA; Nordic Naturals, Watsonville, CA) twice daily for 30 days while consuming a self-selected diet. On days 25-30 of the supplement period, the subjects again consumed the same controlled low-oxalate diet for 5 days and collected 24-hour urine specimens on days 3-5. The same urinary parameters were measured. Statistical analyses included repeated-measures analysis of variance and the Student *t* test.

## RESULTS

A comparison of the self-selected dietary phase, controlled dietary phase without fish oil supplementation, and controlled dietary phase with fish oil supplementation revealed no significant differences in urinary volume, creatinine, sodium, citrate, urea nitrogen, phosphate, or calcium excretions, nor was a significant difference found in the Tiselius index for calcium oxalate. Analyses of variance of daily oxalate, potassium, magnesium, and uric acid excretions were significant ($P < .05$). There was a significant decrease in oxalate, magnesium, and potassium excretions between the self-selected diet and both controlled diet phases ($P < .05$) but no significant difference between the controlled diet phases before and after fish oil supplementation (Table 2). Uric acid excretion was significantly higher on the controlled diets compared with the self-selected diet (<0.05); however, there were no differences between the controlled diet phases with and without fish oil supplementation. Table 2 lists the mean analyte excretion during each study phase.

## COMMENT

A number of investigators have reported that the administration of fish oil supplements promotes a reduction in urinary oxalate excretion. Buck et al[8] treated 12 recurrent hypercalciuric stone formers with 1800-mg EPA and 1200-mg DHA daily for 8 weeks. Urinary calcium and oxalate excretions significantly decreased after administration of fish oil supplements, but the diets were not controlled in this study. Baggio et al[7] noted that urinary calcium and oxalate excretions declined in a study in which 24 recurrent calcium oxalate stone formers ingested 850 mg of omega-3 fatty acid ethyl esters 3 times daily for 30 days. Again, dietary components were not strictly controlled in this study. Siener et al[9] studied 15 healthy subjects who consumed a standardized diet for 5 days, a self-selected diet for 20 days, and a standardized diet again for 5 days. Each participant took 900-mg EPA and 600-mg DHA daily for the last 25 days of the study. The average standardized diet consisted of 2237 kilocalories, 68-g protein, 297-g carbohydrate, 83-g fat, 35-g fiber, 3502-mg potassium, 982-mg calcium, 359-mg magnesium, 2085-mg sodium, 1220-mg phosphorus, 197-mg oxalate, and 3734-mL fluid daily. Results revealed significantly decreased oxalate excretion (13%) and urinary calcium oxalate supersaturation. Similar to the findings of our study, calcium excretion was not significantly affected.

Our results suggest that fish oil supplementation does not have a profound effect on the contribution of endogenous oxalate synthesis to the urinary oxalate pool in healthy individuals with normal baseline urinary oxalate excretion. It could be that the mechanisms proposed by Siener et al, alterations in renal secretion of oxalate or a reduction in net gastrointestinal oxalate absorption, are valid.[9] Perhaps, the responses would be different in a diseased cohort. Our subjects may have had low levels of oxidative stress. Their urinary analyte profile while on a self-selected diet is reflective of healthy eating habits as indicated by higher urinary potassium and magnesium excretion. The response may have been different in calcium oxalate stone formers, especially those with increased oxalate excretion or increased oxidative stress. Therefore, similar studies should be considered in such subjects.

We recognize that our study has certain limitations. Our cohort size was relatively small, but the number is comparable to that of Siener et al.[9] In addition, we measured neither the plasma levels of fatty acids in red blood cell membranes to assess compliance with the fish oil supplement regimen nor the markers of oxidative stress.

## CONCLUSION

It appears that fish oil supplementation does not reduce endogenous oxalate synthesis in healthy non–stone-forming subjects.